

United States Patent Application

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Of

10

Gerhard Jaehne, Volker Krone, Martin Bickel, and Matthias Gossel

For

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C2-substituted idan-1-ols and their derivatives, processes for their preparation and their use as pharmaceuticals

This application claims the benefit of foreign priority under 35 U.S.C. §119 of German patent application no. 10142667.4, filed on August 31, 2001, the contents of which are expressly incorporated by reference herein.

5 Description

C2-substituted indan-1-ols and their derivatives, processes for their preparation and their use as pharmaceuticals.

- 10 Other applications that describe similar compounds and methods of using these compounds include: 1) "Use of C2-substituted indan-1-one systems for preparing medicaments for the prophylaxis or treatment of obesity" of Gerhard Jaehne, Volker Krone, Martin Bickel, and Matthias Gossel filed August 31, 2002, Attorney Docket Number 02481.1797; 2) "C2-substituted indan-1-ones and their
- 15 derivatives, processes for their preparation and their use as pharmaceuticals" of Gerhard Jaehne, Volker Krone, Martin Bickel, and Matthias Gossel filed August 31, 2002, Attorney Docket Number 02481.1795; and 3) "Use of C2-substituted indan-1-ol systems for preparing medicaments for the prophylaxis or treatment of obesity" of Gerhard Jaehne, Volker Krone, Martin Bickel, and Matthias Gossel filed
- 20 August 31, 2002, Attorney Docket Number 02481.1800; all of which are hereby incorporated by reference.

Embodiments of the invention relate to C2-substituted indan-1-ols and their derivatives and also their physiologically acceptable salts and physiologically

25 functional derivatives.

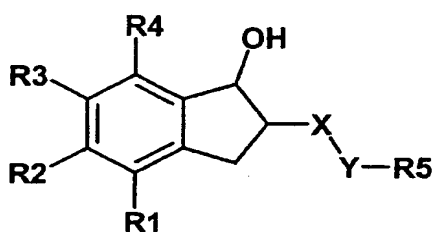
EP 0009554 discloses indan-1-one and -1-ol derivatives as herbicides and analgesics.

- 30 EP 0313296 discloses indan-1-one and -1-ol derivatives as pharmaceuticals for asthma.

WO 97/20806 discloses cyclopentyl-substituted indan-1-one derivatives having inter alia antiinflammatory action.

In one embodiment, an object of the present invention is to provide compounds which can be used for reducing the weight in mammals and which are suitable for preventing and treating obesity.

Embodiments of the invention also relate to compounds of the formula (I)



in which

A)

15 R1 to R4 are H;

X is S, SO, or SO<sub>2</sub>;

Y is (CH<sub>2</sub>)<sub>p</sub>, where p is 0, 1, 2 or 3;

20

R5 is CF<sub>3</sub>, (C<sub>2</sub>-C<sub>18</sub>)-alkyl, (C<sub>3</sub>-C<sub>4</sub>)-cycloalkyl, or (C<sub>6</sub>-C<sub>8</sub>)-cycloalkyl, wherein the alkyl or cycloalkyl groups in each case have zero to seven hydrogen atoms replaced by fluorine;

25

(CH<sub>2</sub>)<sub>r</sub>-COR<sub>6</sub>, where r is 1-6 and R<sub>6</sub> is OH, O-(C<sub>1</sub>-C<sub>6</sub>)-alkyl or NH<sub>2</sub>;

CH<sub>2</sub>-CH(NHR<sub>7</sub>)-COR<sub>8</sub>, where R<sub>7</sub> is H, C(O)-(C<sub>1</sub>-C<sub>4</sub>)-alkyl or C(O)O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl and R<sub>8</sub> is OH, O-(C<sub>1</sub>-C<sub>6</sub>)-alkyl or NH<sub>2</sub>;

phenyl, 1- or 2-naphthyl, biphenyl or a heterocyclic radical, where the rings or ring systems are unsubstituted or substituted one or two times by

O(C<sub>1</sub>-C<sub>8</sub>)-alkyl, O(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, O-CO-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, O-CO-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, S(O)<sub>0-2</sub>(C<sub>1</sub>-C<sub>8</sub>)-alkyl, S(O)<sub>0-2</sub>(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, NH<sub>2</sub>, NH-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, NH-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, N[(C<sub>1</sub>-C<sub>8</sub>)-alkyl]<sub>2</sub>, N[(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl]<sub>2</sub>, NH-CO-(C<sub>2</sub>-C<sub>8</sub>)-alkyl, NH-CO-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, SO<sub>3</sub>H, SO<sub>2</sub>-NH<sub>2</sub>, SO<sub>2</sub>-NH-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, SO<sub>2</sub>-NH-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, NH-SO<sub>2</sub>-NH<sub>2</sub>, NH-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, NH-SO<sub>2</sub>-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, O-CH<sub>2</sub>-COOH, O-CH<sub>2</sub>-CO-O(C<sub>1</sub>-C<sub>8</sub>)-alkyl, COOH, CO-O(C<sub>1</sub>-C<sub>8</sub>)-alkyl, CO-O-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, CO-NH<sub>2</sub>, CO-NH(C<sub>1</sub>-C<sub>8</sub>)-alkyl, CO-N[(C<sub>1</sub>-C<sub>8</sub>)-alkyl]<sub>2</sub>, (C<sub>1</sub>-C<sub>8</sub>)-alkyl, or (C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, wherein the alkyl or cycloalkyl groups in each case have zero to seven hydrogen atoms independently replaced by fluorine, or

F, Cl, Br, I, or CN;

with the proviso that R<sub>5</sub> is not unsubstituted phenyl, 4-fluorophenyl, 4-bromophenyl, 4-chlorophenyl, 3-methylphenyl, 4-methylphenyl, 4-methoxyphenyl, 4-n-butylphenyl, 4-t-butylphenyl, 2-aminophenyl, 2-nitrophenyl or C<sub>12</sub>-alkyl;

or

B)

R<sub>1</sub>, R<sub>4</sub> independently of one another are

H, F, Cl, Br, I, CN, N<sub>3</sub>, NO<sub>2</sub>, OH, O(C<sub>1</sub>-C<sub>8</sub>)-alkyl, O(C<sub>3</sub>-C<sub>4</sub> and C<sub>6</sub>-C<sub>8</sub>)-cycloalkyl, O-CH<sub>2</sub>-phenyl, O-phenyl, O-CO-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, O-CO-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, S(O)<sub>0-2</sub>(C<sub>1</sub>-C<sub>8</sub>)-alkyl, S(O)<sub>0-2</sub>(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, NH<sub>2</sub>, NH-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, NH-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, N[(C<sub>1</sub>-C<sub>8</sub>)-alkyl]<sub>2</sub>, N[(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl]<sub>2</sub>, NH-CO-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, NH-CO-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, SO<sub>3</sub>H, SO<sub>2</sub>-NH<sub>2</sub>, SO<sub>2</sub>-NH-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, SO<sub>2</sub>-NH-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, NH-SO<sub>2</sub>-NH<sub>2</sub>, NH-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, NH-SO<sub>2</sub>-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, O-CH<sub>2</sub>-

COOH, O-CH<sub>2</sub>-CO-O(C<sub>1</sub>-C<sub>8</sub>)-alkyl, COOH, CO-O(C<sub>1</sub>-C<sub>8</sub>)-alkyl, CO-O-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, CO-NH<sub>2</sub>, CO-NH(C<sub>1</sub>-C<sub>8</sub>)-alkyl, CO-N[(C<sub>1</sub>-C<sub>8</sub>)-alkyl]<sub>2</sub>, (C<sub>1</sub>-C<sub>8</sub>)-alkyl, (C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, (C<sub>2</sub>-C<sub>8</sub>)-alkenyl, or (C<sub>2</sub>-C<sub>8</sub>)-alkynyl, where in the alkyl, cycloalkyl, alkenyl and alkynyl groups in each case have zero to seven hydrogen atoms replaced by fluorine, or one hydrogen replaced by OH, OC(O)CH<sub>3</sub>, O-CH<sub>2</sub>-Ph, NH<sub>2</sub>, NH-CO-CH<sub>3</sub> or N(COOCH<sub>2</sub>Ph)<sub>2</sub>; or

phenyl, 1- or 2-naphthyl,

5-tetrazolyl, 1-[(C<sub>1</sub>-C<sub>6</sub>)-alkyl]-5-tetrazolyl, 2-[(C<sub>1</sub>-C<sub>6</sub>)-alkyl]-5-tetrazolyl, 1-imidazolyl,

1- or 4-[1,2,4]triazolyl,

2- or 3-thienyl,

2- or 3-furyl,

2-, 3- or 4-pyridyl,

2-, 4- or 5-oxazolyl,

3-, 4- or 5-isoxazolyl,

2-, 4- or 5-thiazolyl, or

3-, 4- or 5-isothiazolyl

where in each case the aryl radical or heterocycle is unsubstituted or substituted one or two times by

F, Cl, Br, CN,

OH, (C<sub>1</sub>-C<sub>4</sub>)-alkyl, CF<sub>3</sub>, O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl,

S(O)<sub>0-2</sub>(C<sub>1</sub>-C<sub>6</sub>)-alkyl, NH<sub>2</sub>, NH-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub>)-alkyl,

COOH, CO-O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, or CO-NH<sub>2</sub> and wherein the alkyl groups in each case have zero to seven hydrogen atoms replaced by fluorine;

R<sub>2</sub>, R<sub>3</sub> independently of one another are

H, F, Cl, Br, I, CN, N<sub>3</sub>, NO<sub>2</sub>, O(C<sub>1</sub>-C<sub>8</sub>)-alkyl, O(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, O-CO-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, O-CO-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, S(O)<sub>0-2</sub>(C<sub>1</sub>-C<sub>8</sub>)-alkyl, S(O)<sub>0-2</sub>(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, NH<sub>2</sub>, NH-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, NH-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, N[(C<sub>1</sub>-C<sub>8</sub>)-alkyl]<sub>2</sub>, N[(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl]<sub>2</sub>, NH-CO-(C<sub>1</sub>-C<sub>8</sub>)-

alkyl, NH-CO-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, SO<sub>3</sub>H, SO<sub>2</sub>-NH<sub>2</sub>, SO<sub>2</sub>-NH-(C<sub>5</sub>-C<sub>8</sub>)-  
 alkyl, SO<sub>2</sub>-NH-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, NH-SO<sub>2</sub>-NH<sub>2</sub>, NH-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>8</sub>)-alkyl,  
 NH-SO<sub>2</sub>-(C<sub>5</sub>-C<sub>8</sub>)-cycloalkyl, O-CH<sub>2</sub>-COOH, O-CH<sub>2</sub>-CO-O(C<sub>1</sub>-C<sub>8</sub>)-alkyl,  
 COOH, CO-O(C<sub>1</sub>-C<sub>8</sub>)-alkyl, CO-O-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, CO-NH<sub>2</sub>, CO-  
 5 NH(C<sub>1</sub>-C<sub>8</sub>)-alkyl, CO-N[(C<sub>1</sub>-C<sub>8</sub>)-alkyl]<sub>2</sub>, (C<sub>1</sub>-C<sub>8</sub>)-alkyl, (C<sub>3</sub>-C<sub>8</sub>)-  
 cycloalkyl, (C<sub>2</sub>-C<sub>8</sub>)-alkenyl, or (C<sub>2</sub>-C<sub>8</sub>)-alkynyl, where in the alkyl,  
 cycloalkyl, alkenyl and alkynyl groups in each case have zero to  
 seven hydrogen atoms replaced by fluorine,  
 or one hydrogen replaced by OH, OC(O)CH<sub>3</sub>, O-CH<sub>2</sub>-Ph, NH<sub>2</sub>, NH-  
 10 CO-CH<sub>3</sub> or N(COOCH<sub>2</sub>Ph)<sub>2</sub>; or

phenyl, 1- or 2-naphthyl,  
 5-tetrazolyl,  
 1-[(C<sub>1</sub>-C<sub>6</sub>)-alkyl]-5-tetrazolyl,  
 15 2-[(C<sub>1</sub>-C<sub>6</sub>)-alkyl]-5-tetrazolyl,  
 1-imidazolyl,  
 1- or 4-[1,2,4]triazolyl,  
 2- or 3-thienyl,  
 2- or 3-furyl,  
 20 2-, 3- or 4-pyridyl,  
 2-, 4- or 5-oxazolyl,  
 3-, 4- or 5-isoxazolyl,  
 2-, 4- or 5-thiazolyl, or  
 3-, 4- or 5-isothiazolyl

25 where the heterocycle is unsubstituted or substituted one or two times  
 by F, Cl, Br, CN, OH, (C<sub>1</sub>-C<sub>4</sub>)-alkyl, CF<sub>3</sub>, O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl,  
 S(O)<sub>0-2</sub>(C<sub>1</sub>-C<sub>6</sub>)-alkyl, NH<sub>2</sub>, NH-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub>)-alkyl,  
 COOH, CO-O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, or CO-NH<sub>2</sub> wherein the alkyl groups in  
 each case have zero to seven hydrogen atoms replaced by fluorine;

30 or R<sub>2</sub> and R<sub>3</sub> together form the group -O-CH<sub>2</sub>-O-;

where in each case at least one of the radicals R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> is different from  
 hydrogen;

X is S, SO, or SO<sub>2</sub>;

Y is (CH<sub>2</sub>)<sub>p</sub>, where p can be 0, 1, 2 or 3;

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R<sub>5</sub> is (C<sub>1</sub>-C<sub>18</sub>)-alkyl, or (C<sub>3</sub>-C<sub>4</sub>- and C<sub>6</sub>-C<sub>8</sub>)-cycloalkyl, wherein the alkyl and cycloalkyl groups in each case have zero to seven hydrogen atoms replaced by fluorine;

10

(CH<sub>2</sub>)<sub>r</sub>-COR<sub>6</sub>, where r is 1-6 and R<sub>6</sub> is OH, O-(C<sub>1</sub>-C<sub>6</sub>)-alkyl or NH<sub>2</sub>;

CH<sub>2</sub>-CH(NHR<sub>7</sub>)-COR<sub>8</sub>, where R<sub>7</sub> is H, C(O)-(C<sub>1</sub>-C<sub>4</sub>)-alkyl or C(O)O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl and R<sub>8</sub> is OH, O-(C<sub>1</sub>-C<sub>6</sub>)-alkyl or NH<sub>2</sub>;

15

phenyl, 1- or 2-naphthyl, biphenyl or a heterocyclic radical, where the rings or ring systems are unsubstituted or substituted one or two times by

O(C<sub>1</sub>-C<sub>8</sub>)-alkyl, O(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, O-CO-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, O-CO-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, S(O)<sub>0-2</sub>(C<sub>1</sub>-C<sub>8</sub>)-alkyl, S(O)<sub>0-2</sub>(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, NH<sub>2</sub>,  
 20 NH-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, NH-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, N[(C<sub>1</sub>-C<sub>8</sub>)-alkyl]<sub>2</sub>, N[(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl]<sub>2</sub>, NH-CO-(C<sub>2</sub>-C<sub>8</sub>)-alkyl, NH-CO-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, SO<sub>3</sub>H, SO<sub>2</sub>-NH<sub>2</sub>, SO<sub>2</sub>-NH-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, SO<sub>2</sub>-NH-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, NH-SO<sub>2</sub>-NH<sub>2</sub>, NH-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, NH-SO<sub>2</sub>-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, O-CH<sub>2</sub>-COOH, O-CH<sub>2</sub>-CO-O(C<sub>1</sub>-C<sub>8</sub>)-alkyl, COOH, CO-O(C<sub>1</sub>-C<sub>8</sub>)-alkyl, CO-O-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, CO-NH<sub>2</sub>, CO-NH(C<sub>1</sub>-C<sub>8</sub>)-alkyl, CO-N[(C<sub>1</sub>-C<sub>8</sub>)-alkyl]<sub>2</sub>, (C<sub>1</sub>-C<sub>8</sub>)-alkyl, or (C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, wherein the alkyl or cycloalkyl groups in each case have zero to seven hydrogen atoms replaced by fluorine; or

25

30

F, Cl, Br, I, or CN;

and their physiologically acceptable salts.

In one embodiment, compounds of the formula I are chosen from

R1, R4 independently of one another are

H, F, Cl, Br, I, CN, N<sub>3</sub>, NO<sub>2</sub>, OH, O(C<sub>1</sub>-C<sub>8</sub>)-alkyl, O(C<sub>3</sub>-C<sub>4</sub> and C<sub>6</sub>-C<sub>8</sub>)-  
 5 cycloalkyl, O-CH<sub>2</sub>-phenyl, O-phenyl, O-CO-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, O-CO-(C<sub>3</sub>-  
 C<sub>8</sub>)-cycloalkyl, S(O)<sub>0-2</sub>(C<sub>1</sub>-C<sub>8</sub>)-alkyl, S(O)<sub>0-2</sub>(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, NH<sub>2</sub>,  
 NH-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, NH-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, N[(C<sub>1</sub>-C<sub>8</sub>)-alkyl]<sub>2</sub>, N[(C<sub>3</sub>-C<sub>8</sub>)-  
 cycloalkyl]<sub>2</sub>, NH-CO-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, NH-CO-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, SO<sub>3</sub>H,  
 SO<sub>2</sub>-NH<sub>2</sub>, SO<sub>2</sub>-NH-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, SO<sub>2</sub>-NH-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, NH-SO<sub>2</sub>-  
 10 NH<sub>2</sub>, NH-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, NH-SO<sub>2</sub>-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, O-CH<sub>2</sub>-  
 COOH, O-CH<sub>2</sub>-CO-O(C<sub>1</sub>-C<sub>8</sub>)-alkyl, COOH, CO-O(C<sub>1</sub>-C<sub>8</sub>)-alkyl, CO-O-  
 (C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, CO-NH<sub>2</sub>, CO-NH(C<sub>1</sub>-C<sub>8</sub>)-alkyl, CO-N[(C<sub>1</sub>-C<sub>8</sub>)-  
 alkyl]<sub>2</sub>, (C<sub>1</sub>-C<sub>8</sub>)-alkyl, (C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, (C<sub>2</sub>-C<sub>8</sub>)-alkenyl, or (C<sub>2</sub>-C<sub>8</sub>)-  
 alkynyl, wherein the alkyl, cycloalkyl, alkenyl and alkynyl groups in  
 15 each case have zero to seven hydrogen atoms replaced by fluorine,  
 or one hydrogen replaced by OH, OC(O)CH<sub>3</sub>, O-CH<sub>2</sub>-Ph, NH<sub>2</sub>, NH-  
 CO-CH<sub>3</sub> or N(COOCH<sub>2</sub>Ph)<sub>2</sub>; or

phenyl, 1- or 2-naphthyl,

20 5-tetrazolyl, 1-[(C<sub>1</sub>-C<sub>6</sub>)-alkyl]-5-tetrazolyl, 2-[(C<sub>1</sub>-C<sub>6</sub>)-alkyl]-5-tetrazolyl,  
 1-imidazolyl,

1- or 4-[1,2,4]triazolyl,

2- or 3-thienyl,

2- or 3-furyl,

25 2-, 3- or 4-pyridyl,

2-, 4- or 5-oxazolyl,

3-, 4- or 5-isoxazolyl,

2-, 4- or 5-thiazolyl, or

3-, 4- or 5-isothiazolyl

30 where in each case the aryl radical or heterocycle is unsubstituted or  
 substituted one or two times by

F, Cl, Br, CN,

OH, (C<sub>1</sub>-C<sub>4</sub>)-alkyl, CF<sub>3</sub>, O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl,

S(O)<sub>0-2</sub>(C<sub>1</sub>-C<sub>6</sub>)-alkyl, NH<sub>2</sub>, NH-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub>)-alkyl,



COOH, CO-O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, or CO-NH<sub>2</sub> and wherein the alkyl groups in each case have zero to seven hydrogen atoms replaced by fluorine;

- 5 R<sub>2</sub>, R<sub>3</sub> independently of one another are  
 H, F, Cl, Br, I, CN, N<sub>3</sub>, NO<sub>2</sub>, O(C<sub>1</sub>-C<sub>8</sub>)-alkyl, O(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, O-  
 CO-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, O-CO-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, S(O)<sub>0-2</sub>(C<sub>1</sub>-C<sub>8</sub>)-alkyl,  
 S(O)<sub>0-2</sub>(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, NH<sub>2</sub>, NH-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, NH-(C<sub>3</sub>-C<sub>8</sub>)-  
 10 cycloalkyl, N[(C<sub>1</sub>-C<sub>8</sub>)-alkyl]<sub>2</sub>, N[(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl]<sub>2</sub>, NH-CO-(C<sub>1</sub>-C<sub>8</sub>)-  
 alkyl, NH-CO-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, SO<sub>3</sub>H, SO<sub>2</sub>-NH<sub>2</sub>, SO<sub>2</sub>-NH-(C<sub>5</sub>-C<sub>8</sub>)-  
 alkyl, SO<sub>2</sub>-NH-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, NH-SO<sub>2</sub>-NH<sub>2</sub>, NH-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>8</sub>)-alkyl,  
 NH-SO<sub>2</sub>-(C<sub>5</sub>-C<sub>8</sub>)-cycloalkyl, O-CH<sub>2</sub>-COOH, O-CH<sub>2</sub>-CO-O(C<sub>1</sub>-C<sub>8</sub>)-alkyl,  
 COOH, CO-O(C<sub>1</sub>-C<sub>8</sub>)-alkyl, CO-O-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, CO-NH<sub>2</sub>, CO-  
 NH(C<sub>1</sub>-C<sub>8</sub>)-alkyl, CO-N[(C<sub>1</sub>-C<sub>8</sub>)-alkyl]<sub>2</sub>, (C<sub>1</sub>-C<sub>8</sub>)-alkyl, (C<sub>3</sub>-C<sub>8</sub>)-  
 15 cycloalkyl, (C<sub>2</sub>-C<sub>8</sub>)-alkenyl, or (C<sub>2</sub>-C<sub>8</sub>)-alkynyl, where in the alkyl,  
 alkenyl, cycloalkyl and alkynyl groups in each case have zero to  
 seven hydrogen atoms replaced by fluorine,  
 or one hydrogen replaced by OH, OC(O)CH<sub>3</sub>, O-CH<sub>2</sub>-Ph, NH<sub>2</sub>, NH-  
 CO-CH<sub>3</sub> or N(COOCH<sub>2</sub>Ph)<sub>2</sub>; or  
 20 phenyl, 1- or 2-naphthyl,  
 5-tetrazolyl,  
 1-[(C<sub>1</sub>-C<sub>6</sub>)-alkyl]-5-tetrazolyl,  
 2-[(C<sub>1</sub>-C<sub>6</sub>)-alkyl]-5-tetrazolyl,  
 25 1-imidazolyl,  
 1- or 4-[1,2,4]triazolyl,  
 2- or 3-thienyl,  
 2- or 3-furyl,  
 2-, 3- or 4-pyridyl,  
 30 2-, 4- or 5-oxazolyl,  
 3-, 4- or 5-isoxazolyl,  
 2-, 4- or 5-thiazolyl, or  
 3-, 4- or 5-isothiazolyl

where the heterocycle is unsubstituted or substituted one or two times by

F, Cl, Br, CN, OH, (C<sub>1</sub>-C<sub>4</sub>)-alkyl, CF<sub>3</sub>, O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl,

S(O)<sub>0-2</sub>(C<sub>1</sub>-C<sub>6</sub>)-alkyl, NH<sub>2</sub>, NH-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub>)-alkyl,

5 COOH, CO-O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, or CO-NH<sub>2</sub> wherein the alkyl groups in each case have zero to seven hydrogen atoms replaced by fluorine;

or R<sub>2</sub> and R<sub>3</sub> together form the group -O-CH<sub>2</sub>-O-;

10 where in each case at least one of the radicals R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> is different from hydrogen;

X is S, SO, or SO<sub>2</sub>;

Y is (CH<sub>2</sub>)<sub>p</sub>, where p can be 0, 1, 2 or 3;

15

R<sub>5</sub> is (C<sub>1</sub>-C<sub>18</sub>)-alkyl, or (C<sub>3</sub>-C<sub>4</sub>- and C<sub>6</sub>-C<sub>8</sub>)-cycloalkyl, wherein the alkyl or cycloalkyl groups in each case have zero to seven hydrogen atoms replaced by fluorine;

20

(CH<sub>2</sub>)<sub>r</sub>-COR<sub>6</sub>, where r is 1-6 and R<sub>6</sub> is OH, O-(C<sub>1</sub>-C<sub>6</sub>)-alkyl or NH<sub>2</sub>;

CH<sub>2</sub>-CH(NHR<sub>7</sub>)-COR<sub>8</sub>, where R<sub>7</sub> is H, C(O)-(C<sub>1</sub>-C<sub>6</sub>)-alkyl or C(O)O-(C<sub>1</sub>-C<sub>6</sub>)-alkyl where R<sub>8</sub> is OH, O-(C<sub>1</sub>-C<sub>6</sub>)-alkyl or NH<sub>2</sub>;

25

phenyl, 1- or 2-naphthyl, biphenyl or a heterocyclic radical, where the rings or ring systems are unsubstituted or substituted one or two times by

O(C<sub>1</sub>-C<sub>8</sub>)-alkyl, O(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, O-CO-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, O-CO-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, S(O)<sub>0-2</sub>(C<sub>1</sub>-C<sub>8</sub>)-alkyl, S(O)<sub>0-2</sub>(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, NH<sub>2</sub>,

30

NH-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, NH-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, N[(C<sub>1</sub>-C<sub>8</sub>)-alkyl]<sub>2</sub>, N[(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl]<sub>2</sub>, NH-CO-(C<sub>2</sub>-C<sub>8</sub>)-alkyl, NH-CO-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, SO<sub>3</sub>H, SO<sub>2</sub>-NH<sub>2</sub>, SO<sub>2</sub>-NH-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, SO<sub>2</sub>-NH-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, NH-SO<sub>2</sub>-NH<sub>2</sub>, NH-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, NH-SO<sub>2</sub>-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, O-CH<sub>2</sub>-

COOH, O-CH<sub>2</sub>-CO-O(C<sub>1</sub>-C<sub>8</sub>)-alkyl, COOH, CO-O(C<sub>1</sub>-C<sub>8</sub>)-alkyl, CO-O-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, CO-NH<sub>2</sub>, CO-NH(C<sub>1</sub>-C<sub>8</sub>)-alkyl, CO-N[(C<sub>1</sub>-C<sub>8</sub>)-alkyl]<sub>2</sub>, (C<sub>1</sub>-C<sub>8</sub>)-alkyl, or (C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, wherein the alkyl or cycloalkyl groups in each case have zero to seven hydrogen atoms replaced by fluorine; or

F, Cl, Br, I, or CN;

and their physiologically acceptable salts.

In another embodiment, the compounds of the formula I are chosen from

R1, R4 independently of one another are H, F, Cl, or Br;

R2, R3 independently of one another are H, F, Cl, Br, CN, CONH<sub>2</sub>, NH-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, O-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, COOH, (C<sub>1</sub>-C<sub>8</sub>)-alkyl, (C<sub>1</sub>-C<sub>8</sub>)-alkenyl, (C<sub>1</sub>-C<sub>8</sub>)-alkynyl, where in the alkyl, alkenyl and alkynyl groups in each case have zero to seven hydrogen atoms replaced by fluorine; or

phenyl, or 1-imidazolyl, where the rings are unsubstituted or substituted one or two times by

F, Cl, Br, CN, OH, (C<sub>1</sub>-C<sub>4</sub>)-alkyl, CF<sub>3</sub>, or O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, wherein the alkyl groups in each case have zero to seven hydrogen atoms replaced by fluorine;

where in each case at least one of the radicals R1, R2, R3 and R4 is different from hydrogen;

X is S, SO, or SO<sub>2</sub>;

Y is (CH<sub>2</sub>)<sub>p</sub>, where p can be 0 or 1;

R5 is (C<sub>1</sub>-C<sub>18</sub>)-alkyl or (C<sub>3</sub>-C<sub>4</sub>- and C<sub>6</sub>-C<sub>8</sub>)-cycloalkyl, where in the alkyl and cycloalkyl groups in each case have zero to seven hydrogen atoms replaced by fluorine;

5 (CH<sub>2</sub>)<sub>r</sub>-CO-O-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, where r is 1-6;

CH<sub>2</sub>-CH(NHR<sub>7</sub>)-COR<sub>8</sub>, where R<sub>7</sub> is H, C(O)-(C<sub>1</sub>-C<sub>4</sub>)-alkyl or C(O)O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl and R<sub>8</sub> is OH, O-(C<sub>1</sub>-C<sub>6</sub>)-alkyl or NH<sub>2</sub>;

10 phenyl, or a heterocyclic radical;

and their physiologically acceptable salts.

15 In one embodiment, the invention relates to compounds of the formula I in the form of their racemates, racemic mixtures and pure enantiomers, and also to their diastereomers and mixtures thereof. As used herein, any stereoisomeric form includes racemates, racemic mixtures and pure enantiomers, and also to their diastereomers and mixtures thereof.

20 The alkyl, alkenyl and alkynyl radicals in the substituents R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> can be straight-chain or branched.

Heterocycle or heterocyclic radical is to be understood as meaning ring systems which, in addition to carbon, also contain heteroatoms, such as, for example, 25 nitrogen, oxygen or sulfur. This definition furthermore includes ring systems in which the heterocycle or heterocyclic radical is fused with benzene rings.

Examples of heterocycles or heterocyclic radicals are:

30 heteroaryls, such as  
benzimidazolyl,  
1-[(C<sub>1</sub>-C<sub>6</sub>)-alkyl]benzimidazolyl,  
imidazolyl,  
2- or 3-thienyl,

2- or 3-furyl,  
benzoxazolyl,  
benzothiazolyl,  
2-, 3- or 4-pyridyl,  
5 pyrimidinyl,  
4-, 5- or 6-pyridazin-2H-yl-3-one,  
4-, 5- or 6-pyridazin-2-(C<sub>1</sub>-C<sub>8</sub>)-alkyl-2H-yl-3-one,  
2-benzyl-4-, -5- or -6-pyridazin-2H-yl-3-one,  
3- or 4-pyridazinyl,  
10 2-, 3-, 4- or 8-quinolinyll,  
1-, 3- or 4-isoquinolinyll,  
1-phthalazinyl,  
3- or 4-cinnolinyll,  
2- or 4-quinazolinyll,  
15 2-pyrazinyl,  
2-quinoxalinyll,  
2-, 4- or 5-oxazolyl,  
3-, 4- or 5-isoxazolyl,  
2-, 4- or 5-thiazolyl,  
20 3-, 4- or 5-isothiazolyl,  
1-[(C<sub>1</sub>-C<sub>6</sub>)-alkyl]-2-, -4- or -5-imidazolyl,  
3-, 4- or 5-pyrazolyl,  
1-[(C<sub>1</sub>-C<sub>6</sub>)-alkyl]-3-, -4- or -5-pyrazolyl,  
1- or 4-[1,2,4]-triazolyl,  
25 4- or 5-[1,2,3]-triazolyl,  
1-[(C<sub>1</sub>-C<sub>6</sub>)-alkyl]-4- or -5-[1,2,3]triazolyl,  
3-, 4- or 7-indolyl,  
N-[(C<sub>1</sub>-C<sub>6</sub>)-alkyl]-3-, -4- or -7-indolyl  
2-[(C<sub>1</sub>-C<sub>6</sub>)-alkyl]-3(2H)-indazolyl,  
30 1-[(C<sub>1</sub>-C<sub>6</sub>)-alkyl]-3(1H)-indazolyl,  
5-tetrazolyl,  
1-[(C<sub>1</sub>-C<sub>6</sub>)-alkyl]-1H-tetrazolyl,  
2-[(C<sub>1</sub>-C<sub>6</sub>)-alkyl]-2H-tetrazolyl.

Pharmaceutically acceptable salts are particularly suitable for medical applications, due to their greater solubility in water compared with the starting or base compounds. Said salts usually have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the invention are salts of inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, metaphosphoric acid, nitric acid and sulfuric acid and also of organic acids such as, for example, acetic acid, benzenesulfonic acid, benzoic acid, citric acid, ethanesulfonic acid, fumaric acid, gluconic acid, glycolic acid, isethionic acid, lactic acid, lactobionic acid, maleic acid, malic acid, methane-sulfonic acid, succinic acid, p-toluenesulfonic acid, tartaric acid and trifluoroacetic acid. For some medicinal purposes, particular preference may be given to using the chlorine salt. Examples of suitable pharmaceutically acceptable basic salts are ammonium salts, alkali metal salts (such as sodium salts and potassium salts) and alkaline earth metal salts (such as magnesium salts and calcium salts).

In one embodiment, salts having a pharmaceutically unacceptable anion are likewise included within the scope of the present invention, for example, as useful intermediates for preparing or purifying pharmaceutically acceptable salts and/or for use in nontherapeutic applications, such as in-vitro applications.

As used herein, treating or treatment includes the treating of, for example, a patient inflicted with a disease or condition, as well as the prevention, prophylaxis, or protective treatment of a patient. Thus, for example, treatment of obesity includes reducing and/or maintaining the weight of a subject who is inflicted with obesity or is susceptible to obesity. The treatment of obesity also includes inhibiting and/or slowing the weight gain of a subject who is inflicted with obesity or is susceptible to obesity. Treatment of obesity also includes treating a subject susceptible to or predisposed to developing obesity, which could include patients in whom obesity has not yet presented as well as patients in whom the disease has been successfully treated but could redevelop or reoccur.

As used herein controlling weight includes reducing and/or maintaining the weight of a subject. Controlling weight also includes inhibiting and/or slowing the weight gain of a subject. Thus, for example, the phrase weight controlling compounds includes weight-reducing compounds.

5

The term "physiologically functional derivative" used herein relates to any physiologically acceptable derivative of an inventive compound, for example an ester which on administration to a mammal, for example humans, is capable of forming (directly or indirectly) a compound of the formula I or an active metabolite thereof.

10

The physiologically functional derivatives also include prodrugs of the compounds of the invention. Such prodrugs may be metabolized in vivo to a compound of the invention. These prodrugs may or may not be active themselves.

15 The physiologically functional derivatives furthermore include, for example, derivatives derived from sugars, such as, glycosides and ribosides, glucuronides, and sulfuric acid esters.

20 The compounds of the invention may also be present in various polymorphous forms, for example as amorphous and crystalline polymorphous forms. All polymorphous forms of the compounds of the invention are included within the scope of the invention.

25 All references to compound(s) of the formula (I) herein refer to a compound/compounds of the formula (I) as described herein and also to their solvates, physiologically functional derivatives, and polymorphs as described herein.

30 In one embodiment, the amount of a compound according to formula (I) used to attain the desired biological effect depends on a number of factors, for example the specific compound selected, the intended use, the type of administration and the clinical state of the patient. In general, the daily dose is in the range from 0.3 mg to 100 mg (typically from 3 mg to 50 mg) per day per kilogram of body

weight, for example 3-10 mg/kg/day. An intravenous dose can be, for example, in the range from 0.3 mg to 1.0 mg/kg and can be administered in a suitable manner as an infusion of 10 ng to 100 ng per kilogram per minute. Suitable infusion solutions for these purposes may contain, for example, from 0.1 ng to 10 mg, typically from 1 ng to 10 mg per milliliter. Individual doses may contain, for example, from 1 mg to 10 g of the active compound. Thus, ampules for injections can contain, for example, from 1 mg to 100 mg, and orally administerable individual dose formulations such as, for example, tablets or capsules can contain, for example, from 1.0 to 1000 mg, typically from 10 to 600 mg. In one embodiment, the use of a compound of formula (I) as a prophylaxis may require a lower amount of a compound of formula (I), but still within the range disclosed above, for the patient of interest

In the case of pharmaceutically acceptable salts, the abovementioned masses relate to the mass of the free compound on which the salt is based. The compound used for the prophylaxis or therapy of the abovementioned conditions may be the compounds according to formula (I) themselves, or, in one embodiment, they are present in the form of a pharmaceutical composition together with an acceptable carrier. In one embodiment, the carrier must be naturally acceptable, in the sense that it is compatible with the other ingredients of said composition and is not harmful to the patient's health. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as an individual dose, for example as a tablet which may contain from 0.05% to 95% by weight of the active compound. Further pharmaceutically active substances may also be present, including further compounds according to formula (I). The pharmaceutical compositions of the invention may be prepared according to any of the known pharmaceutical methods which essentially comprise mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

Pharmaceutical compositions of the invention are those which are suitable for oral, rectal, topical, peroral (e.g. sublingual) and parenteral (e.g. subcutaneous, intramuscular, intradermal or intravenous) administration, although the most suitable manner of administration depends in each individual case on the nature



and severity of the condition to be treated and on the nature of the compound according to formula (I) used in each case. Sugar-coated formulations and sugar-coated delayed-release formulations, too, are included within the scope of the invention. In one embodiment, preference is given to acid-resistant and enteric  
5 formulations. Suitable enteric coatings include cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

Suitable pharmaceutical compounds for oral administration may be present in  
10 separate units as, for example, capsules, cachets, lozenges or tablets, which in each case contain a particular amount of the compound according to formula (I); as powders or granules; as solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. As already mentioned, said compositions can be prepared according to any suitable pharmaceutical method  
15 which includes a step in which the active compound and the carrier (which may comprise one or more additional components) are contacted. In general, the compositions are prepared by uniform and homogeneous mixing of the active compound with a liquid and/or finely dispersed solid carrier, after which the product is shaped, if necessary. Thus a tablet, for example, may be prepared by  
20 pressing or shaping a powder or granules of the compound, where appropriate with one or more additional components. Pressed tablets can be prepared by tableting the compound in free-flowing form, for example a powder or granules, mixed, where appropriate, with a binder, lubricant, inert diluent and/or one or more surface active/dispersing agents in a suitable machine. Shaped tablets can be  
25 prepared by shaping the pulverulent compound, moistened with an inert liquid diluent, in a suitable machine.

Pharmaceutical compositions which are suitable for peroral (sublingual) administration include lozenges which contain a compound according to formula  
30 (I) with a flavoring, usually sucrose and gum arabic or tragacanth, and pastilles which comprise the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

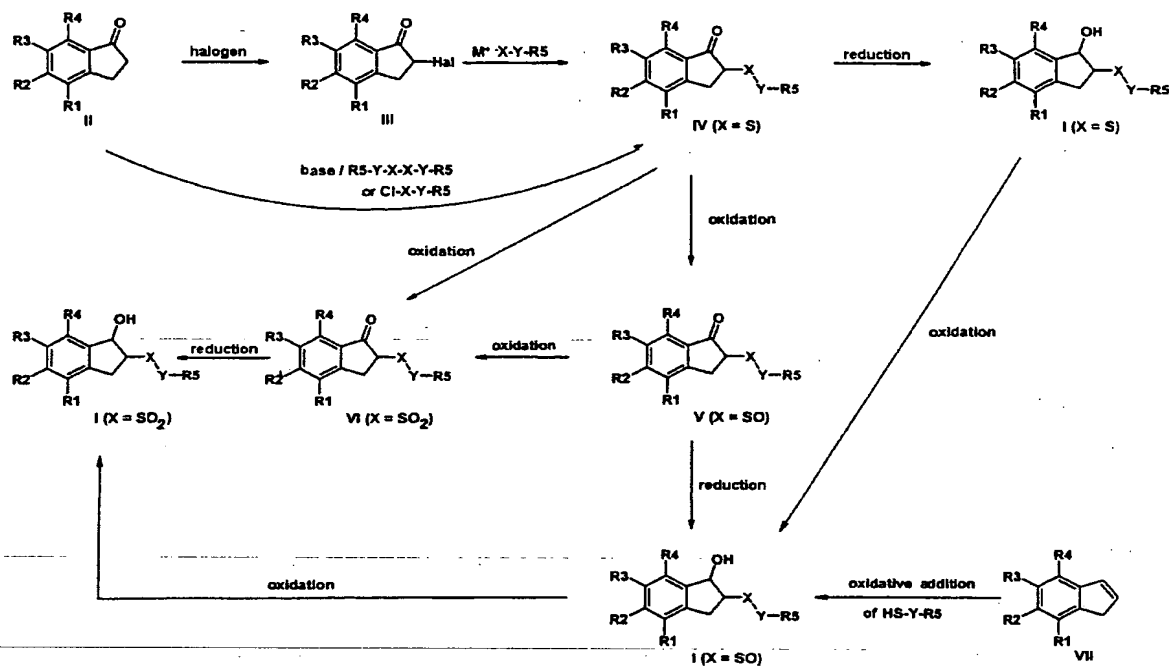
Suitable pharmaceutical compositions for parenteral administration may, for example, comprise sterile aqueous preparations of a compound according to formula (I) which are isotonic with the blood of the intended recipient. These preparations may be administered intravenously, although they may also be administered subcutaneously, intramuscularly or intradermally as an injection. Said preparations may be prepared by mixing the compound with water and rendering the obtained solution sterile and isotonic with the blood. Injectable compositions of the invention generally contain from 0.1 to 5% by weight of the active compound.

Suitable pharmaceutical compositions for rectal administration are present as individual dose suppositories. These may be prepared by mixing a compound according to formula (I) with one or more conventional solid carriers, for example cocoa butter, and shaping the resulting mixture.

Suitable pharmaceutical compositions for topical application to the skin may be present as ointment, cream, lotion, paste, spray, aerosol or oil. Carriers which may be used include, for example, petroleum jelly, lanolin, polyethylene glycols, alcohols and combinations of two or more of these substances. In one embodiment, the active compound is present at a concentration ranging from 0.1 to 15%, for example from 0.5 to 2%, by weight of the composition.

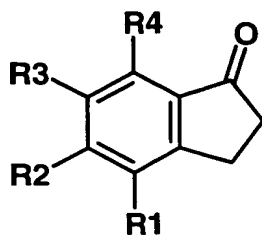
Transdermal administration is also possible. Suitable pharmaceutical compositions for transdermal administration may be present as individual patches which are suitable for long-term close contact with the epidermis of the patient. Such patches suitably contain the active compound in an optionally buffered aqueous solution, dissolved and/or dispersed in an adhesive or dispersed in a polymer. A suitable active compound concentration is from approx. 1% to 35%, preferably approx. 3% to 15%. A particular possibility is the release of the active compound by electro-transport or iontophoresis, as described, for example, in *Pharmaceutical Research*, 2(6): 318 (1986).

The invention furthermore provides a process for preparing the compounds of the formula I which comprises obtaining the compounds of the formula I by proceeding according to the reaction schemes below:



5

To this end, compounds of the formula II,



Formula II

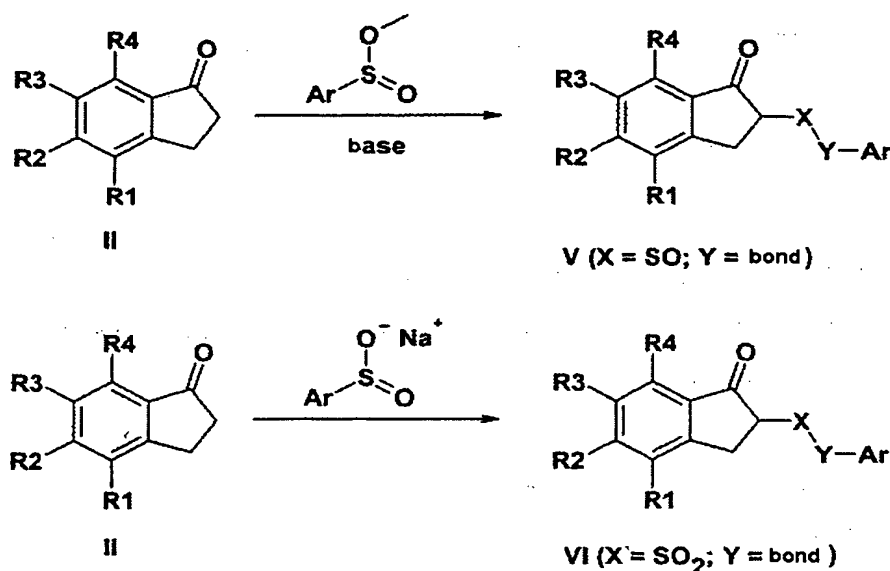
5 in which R1, R2, R3 and R4 are as defined above are converted with a halogen, such as, for example, bromine or chlorine, into a compound of the formula III. The compounds of the formula III are converted further with metal salts of thiols of the formula H-X-Y-R5, where X is sulfur and Y and R5 are as defined above into compounds of the formula IV where X = S. These metal salts can be employed as  
10 such or they can be generated in solution in situ from the thiol and a base, such as, for example, aqueous sodium hydroxide.

On the other hand, in another embodiment, compounds of the formula IV where X = S can be obtained by reacting compounds of the formula II with a base, such as,  
15 for example, lithium diisopropylamide, for example in tetrahydrofuran, and with a disulfide of the formula R5-Y-X-X-Y-R5 in which R5 and Y are as defined above and X = S; alternatively, instead of the disulfide, it is also possible to use a sulphenyl chloride of the formula Cl-X-Y-R5 where X = S and Y and R5 are as defined above (see, for example, D. Seebach et al.; Chem. Ber. **109**, 1601-1616 (1976)).

20 Compounds of the formula V in which X = SO can be prepared, for example, by selective oxidation of the compound of the formula IV in which X = S, using one equivalent of peroxytrifluoroacetic acid (C. G. Venier et al.; J. Org. Chem. **47**, 3773 (1982)). The preparation of the sulfoxides from the sulfides can also be carried out  
25 using manganese dioxide or chromic acid (D. Edwards et al.; J. Chem. Soc. **1954**, 3272). Furthermore suitable for this oxidation is hydrogen peroxide in acetic anhydride (A. V. Sviridova et al.; J. Org. Chem (Russ), English Transl.; **7**, 2577 (1971)).

Compounds of the formula VI in which  $X = SO_2$  can be obtained by oxidation using, for example,  $2KHSO_5 \times KHSO_4 \times K_2SO_4$  (Oxone), either from compounds of the formula IV in which  $X = S$  or from compounds of the formula V in which  $X = SO$  (see, for example, M. Hudlický, *Oxidations in Organic Chemistry*, ACS Monograph 186, American Chemical Society, Washington, DC, 1990).

Compounds of the formula V in which  $X = SO$  or of the formula VI in which  $X = SO_2$  and  $Y = \text{a bond}$  ( $= (CH_2)_m$  where  $m = 0$ ) can also, alternatively, be prepared according to the scheme below (shown for the preparation of the aryl sulfoxides (H. J. Monteiro et al.; *Tetrahedron Letters* **11**, 921-924 (1975) and aryl sulfones (A. K. Maiti et al.; *Tetrahedron* **50**, 10483-10490 (1994)):



By reduction with, for example, lithium aluminum hydride or sodium borohydride, the ketones of the formula IV in which  $X = S$  can be converted into the alcohols of the formula I in which  $X = S$ . In a similar manner, the compounds of the formula V in which  $X = SO$  can be converted into the compounds of the formula I in which  $X = SO$ , and the compounds of the formula VI in which  $X = SO_2$  can likewise be converted into compounds of the formula I in which  $X = SO_2$ . Furthermore, compounds of the formula I in which  $X = SO$  can be converted by oxidation into compounds of the formula I in which  $X = SO_2$ .

Indenes of the formula VII can be converted by oxidative addition of compounds of the formula HX-Y-R5 in which X = S in compounds of the formula I in which X = SO (see, for example, J.F. Ford et al. (Tetrahedron 4, 325-336 (1958))).

- 5 Inorganic acids suitable for forming salts are, for example: hydrohalic acids, such as hydrochloric acid and hydrobromic acid, and also sulfuric acid, phosphoric acid and amidosulfonic acid.

- 10 Organic acids suitable for salt formation which may be mentioned are, for example: formic acid, acetic acid, benzoic acid, p-toluenesulfonic acid, benzenesulfonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, citric acid, L-ascorbic acid, salicylic acid, isethionic acid, methanesulfonic acid, trifluoromethanesulfonic acid, 1,2-benzisothiazol-3(2H)-one, 6-methyl-1,2,3-oxathiazin-4(3H)-one 2,2-dioxide.

15

The examples shown below serve to illustrate the invention without limiting it. The melting points or decomposition points (m.p.) measured are uncorrected and generally depend on the heating rate.

- 20 The retention times given in the table below refer to the following methods for determination:

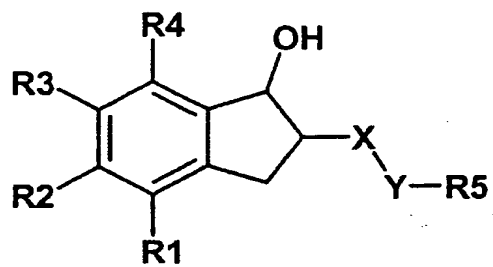
Method A: Column: Merck, LiChroCart 55-2, PuroSpher STAR, RP 18 e; measured at 254 nm; gradient: solvent A acetonitrile/water 90:10 + 0.5% formic acid; solvent B acetonitrile/water 10:90 + 0.5 % formic acid; flow rate: 0.750 ml/min; time (min)/solvent B (%): 0.00/95.0, 0.50/95.0, 1.75/5.0, 4.25/5.0, 4.50/95.0, 5.00/95.0; temperature: 40°C:

- 25

Method B: column: YMC J'sphere, 33x2, ODS H 80 4 µ; measured at 254 nm; gradient: solvent A acetonitrile + 0.5% formic acid; solvent B water + 0.5% formic acid; flow rate: 1.00 ml/min; time (min)/solvent B (%): 0.00/90.0, 2.50/5.0, 3.30/5.0, 3.35/90.0; temperature: 30°C:

30

Table 1: Examples



Formula I

| Example | R1 | R2                                      | R3   | R4 | X               | Y               | R5  | m.p.[°C]                                       |
|---------|----|---|--|----|-----------------|-----------------|---|--|
| 1       | H  | Cl                                      | H  | H  | SO <sub>2</sub> | -               | CH <sub>3</sub>   | 163  |
| 2       | H  | Cl                                      | H  | H  | SO <sub>2</sub> | -               | CH(CH <sub>3</sub> ) <sub>2</sub>                                   | wax  |
| 3       | H  | Cl                                      | H  | H  | SO <sub>2</sub> | -               | CH <sub>2</sub> -CH <sub>3</sub>                                    | 145  |
|         |    |   |  |    |                 |                 |   |  |
|         |    |   |  |    |                 |                 |   | [MH <sup>+</sup> ]                             |
| 4       | H  | Cl                                      | H  | H  | S               | -               | CH <sub>3</sub>   | 197.1<br>(MH <sup>+</sup> - H <sub>2</sub> O)  |
| 5       | H  | Cl                                      | H  | H  | SO              | -               | CH <sub>3</sub>   | 231.02   |
|         |    |   |  |    |                 |                 |   |  |
|         |    |   |  |    |                 |                 |   | Retention<br>time in min<br>(method A or<br>B) |
| 6       | H  | CF <sub>3</sub>                         | H  | H  | SO <sub>2</sub> | -               | CH <sub>3</sub>   | 1.853<br>(B)                                   |
| 7       | H  | Cl                                      | H  | H  | S               | CH <sub>2</sub> | CH(NHCOCH <sub>3</sub> )<br>(COOH)                                  | 1.755<br>(B)                                   |
| 8       | H  | Cl                                      | H  | H  | SO <sub>2</sub> | CH <sub>2</sub> | CH <sub>2</sub> -CH <sub>3</sub>                                    | 1.938<br>(B)                                   |
| 9       | H  | Cl                                      | H  | H  | S               | CH <sub>2</sub> | CH <sub>2</sub> -CH <sub>3</sub>                                    | 2.231<br>(B)                                   |
| 10      | H  | Cl                                      | H  | H  | SO <sub>2</sub> | CH <sub>2</sub> | C <sub>6</sub> H <sub>5</sub>                                       | 2.191<br>(B)                                   |
| 11      | H  | Cl                                      | H  | H  | SO <sub>2</sub> | -               | pyrimidin-2-yl  | 1.399 (B)                                      |
| 12      | H  | Cl                                      | H  | H  | SO <sub>2</sub> | -               | pyridin-2-yl  | 1.992 (B)                                      |
| 13      | H  | H                                       | H  | H  | S               | -               | benzoxazol-2-yl   | 2.084 (B)                                      |
| 14      | H  | H                                       | C <sub>6</sub> H <sub>4</sub> -<br>4-CF <sub>3</sub> | H  | S               | CH <sub>2</sub> | C <sub>6</sub> H <sub>5</sub>                                       | 3.130 (B)                                      |
| 15      | H  | H                                       | C <sub>6</sub> H <sub>4</sub> -<br>4-CF <sub>3</sub> | H  | SO <sub>2</sub> | -               | CH <sub>3</sub>   | 3.307 (B)                                      |
| 16      | Br | H                                       | H  | H  | SO <sub>2</sub> | -               | CH <sub>3</sub>   | 1.682 (B)                                      |
| 17      | H  | NH-SO <sub>2</sub> -<br>CH <sub>3</sub> | H  | H  | S               | -               | C(CH <sub>3</sub> ) <sub>2</sub> CH(NHCO<br>CH <sub>3</sub> )(COOH) | 1.577 (B)                                      |
| 18      | H  | Cl                                      | H  | H  | SO <sub>2</sub> | CH <sub>2</sub> | CH(NH <sub>2</sub> )(COOH)  | 1.831 (B)                                      |



|    |   |    |  |   |   |                 |   |  |
|----|---|----|--|---|---|-----------------|---|--|
| 19 | H | Cl | H  | H | S | CH <sub>2</sub> | CH(NH <sub>2</sub> )(COOCH <sub>3</sub> ) | 2.567 (B)                                      |
|    |   |    |  |   |   |                 |   |  |
|    |   |    |  |   |   |                 |   | [MH <sup>+</sup> ]                             |
| 20 | H | H  | C <sub>6</sub> H <sub>4</sub> -<br>4-CF <sub>3</sub> | H | S | -               | CH(CH <sub>3</sub> ) <sub>2</sub>         | 335.08 (MH <sup>+</sup> -<br>H <sub>2</sub> O) |

In one embodiment, the compounds of the formula I are distinguished by beneficial actions on the metabolism of lipids, and they are particularly suitable for weight reduction and, after weight reduction, for maintaining a reduced weight in

5 mammals and as anorectic agents. The compounds may be distinguished by their low toxicity and their few side effects. The compounds may be employed alone or in combination with other weight-reducing or anorectic active compounds. Further

anorectic active compounds of this kind are mentioned, for example, in the Rote Liste, Chapter 01 under weight-reducing agents/appetite suppressants, herein  
10 incorporated by reference, and may also include those active compounds which increase the energy turnover of the organism and thus lead to weight reduction or else those which influence the general metabolism of said organism such that increased calorie intake does not cause an enlargement of the fat depots and a normal calorie intake causes a reduction in the fat depots of said organism. The  
15 compounds may be suitable for the prophylaxis and, in particular, for the treatment of problems of excess weight or obesity. The compounds furthermore may also be suitable for the prophylaxis and, in particular, for the treatment of type II diabetes, of arteriosclerosis and for the normalization of lipid metabolism and for the treatment of high blood pressure.

20

In a further aspect of the invention, the compounds of the formula I may be administered in combination with one or more further pharmacologically active substances which may be chosen, for example, from antidiabetics, antiadipose agents, blood-pressure-lowering active compounds, lipid reducers and active  
25 compounds for the treatment and/or prevention of complications caused by diabetes or associated with diabetes. One of skill in the art, based on the activity and the known amounts for administration of the above compounds, will be able to

readily determine the amounts of these compounds that are useful in a combination therapy with the compounds of the invention.

Suitable antidiabetics include insulins, amylin, GLP-1 and GLP-2 derivatives such as, for example, those disclosed by Novo Nordisk A/S in WO 98/08871 and also  
5 oral hypoglycemic active compounds.

In one embodiment, said oral hypoglycemic active compounds include sulfonyl ureas, biguanides, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, glucagon receptor antagonists, GLP-1 agonists, potassium  
10 channel openers such as, for example, those disclosed by Novo Nordisk A/S in WO 97/26265 and WO 99/03861, insulin sensitizers, activators of insulin receptor kinase, inhibitors of liver enzymes involved in the stimulation of gluconeogenesis and/or glycogenolysis, for example glycogen phosphorylase inhibitors, modulators of glucose uptake and glucose elimination, lipid metabolism-modifying compounds  
15 such as antihyperlipidemic active compounds and antilipidemic active compounds, for example HMGCoA-reductase inhibitors, inhibitors of cholesterol transport/cholesterol uptake, inhibitors of the reabsorption of bile acid or inhibitors of microsomal triglyceride transfer protein (MTP), compounds which reduce food intake, PPAR and RXR agonists and active compounds which act on the ATP-dependent potassium channel of beta cells.

20 In one embodiment of the present invention, the present compounds are administered in combination with insulin.

In another embodiment, the compounds of the invention are administered in combination with a sulfonylurea such as, for example, tolbutamide, glibenclamide, glimepiride, glipizide, gliquidone, glisoxepide, glibornuride or gliclazide.

25 In another embodiment, the compounds of the present invention are administered in combination with a biguanide such as, for example, metformin.

In another embodiment, the compounds of the present invention are administered in combination with a meglitinide such as, for example, repaglinide.

In yet another embodiment, the compounds of the present invention are administered in combination with a thiazolidinedione such as, for example, troglitazone, ciglitazone, pioglitazone, rosiglitazone or the compounds disclosed by Dr. Reddy's Research Foundation in WO 97/41097, in particular 5-[[4-[(3,4-dihydro-3-methyl-4-oxo-2-quinazolinylmethoxy)phenyl]methyl]-2,4-thiazolidinedione.

In yet another embodiment, the compounds of the present invention are administered in combination with a monoamine oxidase inhibitor such as disclosed, for example, in WO 01/12176. Particularly suitable for this purpose are [3(S),3a(S)]-3-methoxymethyl-7-[4,4,4-trifluorobutoxy]-3,3a,4,5-tetrahydro-1H-oxazolo[3,4-a]quinolin-1-one, (R)-5-(methoxymethyl)-3-[6-(4,4,4-trifluorobutoxy)benzofuran-3-yl]oxazolidin-2-one or (R)-5-(methoxymethyl)-3-[6-cyclopropylmethoxybenzofuran-3-yl]oxazolidin-2-one.

In another embodiment, the compounds of the present invention are administered in combination with an  $\alpha$ -glucosidase inhibitor such as, for example, miglitol or acarbose.

In yet another embodiment, the present compounds are administered in combination with an hCNTF (human ciliary neurotrophic factor) or derivatives thereof, such as, for example, CNTF<sub>AX15</sub> or modified CNTF<sub>AX15</sub>, such as disclosed, for example, in Lambert et al., PNAS **98**, 4652-4657.

In another embodiment, the compounds of the present invention are administered in combination with an active compound which acts on the ATP-dependent potassium channel of the beta cells, such as, for example, tolbutamide, glibenclamide, glimepiride, glipizide, gliclazide or repaglinide.

In yet another embodiment, the compounds of the present invention are administered in combination with an antihyperlipidemic active compound or an antilipidemic active compound such as, for example, cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, probucol, ezetimibe or dextrothyroxine.

In another embodiment, the compounds of the present invention are administered in combination with more than one of the aforementioned compounds, for example in combination with a sulfonylurea and metformin, a sulfonylurea and acarbose, repaglinide and metformin, insulin and a sulfonylurea, insulin and metformin,

5 insulin and troglitazone, insulin and lovastatin, etc.

Furthermore, the compounds of the invention may be administered in combination with one or more antiadipose agents or appetite-controlling active compounds.

Such active compounds may be selected from the group consisting of CART agonists, NPY antagonists, melanocortin 3 or 4 (MC3 or MC4) agonists, melanin-concentrating hormone (MCH) antagonists, orexin antagonists, H3 agonists, TNF agonists, CRF agonists, CRF BP antagonists, urocortin agonists,  $\beta$ 3 adrenoceptor agonists, CCK agonists, serotonin re-uptake inhibitors, mixed serotonin and noradrenalin reuptake inhibitors, 5HT modulators, bombesin agonists, galanin antagonists, glucocorticoid receptor modulators, growth hormone, growth-

10 hormone-releasing compounds, TRH agonists, uncoupling protein 2 or 3 modulators, leptin receptor agonists, leptin mimetics, dopamine agonists (bromocriptine, dorexin), lipase/amylase inhibitors, cannabinoid receptor 1 antagonists, modulators of acylation-stimulating protein (ASP), PPAR modulators, RXR modulators or TR- $\beta$  agonists.

20 In one embodiment of the invention, the antiadipose agent is leptin or modified leptin.

In another embodiment, the antiadipose agent is dexamphetamine or amphetamine.

In another embodiment, the antiadipose agent is fenfluramine or dexfenfluramine.

25 In yet another embodiment, the antiadipose agent is sibutramine or the mono- and bis-demethylated active metabolite of sibutramine.

In another embodiment, the antiadipose agent is orlistate.

In another embodiment, the antiadipose agent is mazindol, diethylpropione or phentermine.

Furthermore, the compounds of the present invention may be administered in combination with one or more antihypertensive active compounds. Examples of  
5 antihypertensive active compounds are betablockers such as alprenolol, atenol, timolol, pindolol, propanolol and metoprolol, ACE (angiotensin-converting enzyme) inhibitors such as, for example, benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and rampril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, nimodipine, diltiazem and verapamil, and also  
10 alphablockers such as doxazosin, urapidil, prazosin and terazosin. Furthermore, reference may be made to Remington: The Science and Practice of Pharmacy, 19th edition, Gennaro, editor, Mack Publishing Co., Easton, PA, 1995.

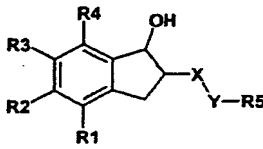
It is self-evident that every suitable combination of the compounds of the invention  
with one or more of the aforementioned compounds and optionally one or more  
15 other pharmacologically active substances is to be regarded as covered by the scope of protection of the present invention.

The activity of the compounds was assayed as follows:

Biological test model:

The anorectic action was tested on female NMRI mice. After removal of feed for  
20 24 hours, the preparation to be tested was administered intraperitoneally (ip) or by gavage (po). The animals were housed singly and, with free access to drinking water, they were offered evaporated milk 30 minutes after administration of the preparation. The consumption of evaporated milk was determined and the general behavior of the animals was monitored every half an hour for 7 hours. The  
25 measured milk consumption was compared to that of vehicle-treated control animals.

Table 2: Anorectic action, measured as a reduction in the cumulative milk consumption by treated animals compared with control animals

| Compound<br>/Example<br><br><br>Formula I | Dose<br>[mg/kg] | Number of<br>animals/<br>cumulative milk<br>consumption<br>by treated<br>animals<br><br>N / [ml] | Number of<br>animals/<br>cumulative milk<br>consumption<br>by untreated<br>control animals<br><br>N / [ml] | Reduction in<br>cumulative milk<br>consumption as<br>% of the control |
|--|-----------------|--|--|---|
| Example 1  | 20              | 5/1.94   | 5/3.86   | 50  |
| Example 4  | 50              | 5/0.70   | 5/4.76   | 85  |

The table indicates that the compounds of the formula I exhibit very good anorectic action.

5

The preparation of some examples is described in detail below; the other compounds of the formula I were obtained analogously:

Example 1:

10 5-Chloro-2-methylsulfonylindan-1-ol:

1. 5-Chloro-2-methylsulfonylindan-1-one:

0.98 g (4 mmol) of 2-bromo-5-chloroindan-1-one and 0.42 g (6 mmol) of sodium thiomethoxide were suspended in 5 ml of ethanol, treated in an ultrasonic bath for 30 minutes and then stirred at room temperature for 90 minutes. The reaction mixture was concentrated under reduced pressure and chromatographed on silica gel using toluene/ethyl acetate 10/1. The eluates were concentrated under reduced pressure, giving 5-chloro-2-methylsulfonylindan-1-one of melting point 90°C.

2. 5-Chloro-2-methylsulfonylindan-1-one:

0.5 g (2.35 mmol) of 5-chloro-2-methylsulfonylindan-1-one was dissolved in 10 ml of methanol; at 0°C, a solution of 4.33 g (7.05 mmol) of 2KHSO<sub>5</sub> x KHSO<sub>4</sub> x K<sub>2</sub>SO<sub>4</sub> in 10 ml of water was added dropwise. The mixture was stirred at room temperature for 5 h; the methanol was distilled off and the aqueous residue was extracted with dichloromethane. The organic phase was separated off, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. This gave 5-chloro-2-methanesulfonylindan-1-one of melting point 197°C.

3. 5-Chloro-2-methylsulfonylindan-1-ol:

0.489 g (2 mmol) of 5-chloro-2-methylsulfonylindan-1-one and 0.095 g (2.5 mmol) of sodium borohydride were suspended in 10 ml of ethanol and placed in an ultrasonic bath for 4 h. The reaction mixture was then acidified with 2N HCl and stirred. The ethanol was distilled off, water and dichloromethane were added to the residue and the mixture was extracted with dichloromethane. The organic phase was separated off, dried over MgSO<sub>4</sub>, filtered and concentrated and the residue was purified chromatographically on silica gel using dichloromethane/methanol 20/1. This gave 5-chloro-2-methylsulfonylindan-1-ol of melting point 163°C.

Example 2:

5-Chloro-2-(propane-2-sulfonyl)indan-1-ol:

200 mg (0.8 mmol) of 5-chloro-2-methylsulfonylindan-1-ol were dissolved in 5 ml of dry tetrahydrofuran. The solution was cooled to -70°C, and under an atmosphere of nitrogen, 0.4 ml (0.8 mmol) of lithium diisopropylamine (2 M solution in tetrahydrofuran) was added dropwise. The reaction solution was stirred at -70°C for 30 min, and 62.2 µl (1 mmol) of methyl iodide were then

added. The reaction mixture was warmed to 0°C, water and then ethyl acetate was added, the organic phase was separated off, dried over magnesium sulfate and filtered and the filtrate was concentrated.

5 Chromatographic purification of the residue (silica gel; heptane/ethyl acetate 1/1) gave 5-chloro-2-(propane-2-sulfonyl)indan-1-ol as a wax-like substance.

Example 3:

10 5-Chloro-2-ethanesulfonylindan-1-ol:

The chromatographic purification described above in example 2 furthermore yielded 5-chloro-2-ethanesulfonylindan-1-ol of melting point 145°C.

15 Example 4:

5-Chloro-2-methylsulfonylindan-1-ol:

20 The compound of example 1 was subjected to a reduction with sodium borohydride. This gave 5-chloro-2-methylsulfonylindan-1-ol of a molecular weight 214.72 (C<sub>10</sub>H<sub>11</sub>ClSO); MS (ESI): 197.1 (MH<sup>+</sup>-H<sub>2</sub>O).

Example 5:

25 The compound of example 5 was obtained from 5-chloro-2-methanesulfonylindan-1-one by reduction with sodium borohydride as described in Example 1-3.

30 Compounds of examples 6-17 were obtained from the corresponding ketones by reduction with sodium borohydride.